BioTherapeutics Research and Development

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Opportunities for Improved Therapies for Hemophilia A and B

- Less frequent dosing (via EHL) will reduce the burden of disease on patients
  - Protein Engineering of Factor VIII and Factor IX
  - Formulation Approaches (e.g., ReFactoAF/Xyntha®)

- Improvement in efficacy and convenience will reduce the burden of disease on patients
  - Differentiated FVIIa with Improved Properties
  - “Zymogen-like” Factor Xa

All approaches must balance any changes in activity vs. thrombogenic and immunogenic potential.
Development of Therapeutic Bypass Agents

- **Hemophilia patients who develop inhibitory antibodies are refractory to replacement therapies**
  - Treatment of inhibitor patients
    - APCC and derivatives: FVIII inhibitor bypass activity (FEIBA)
    - Recombinant FVIIa
      - Activates coagulation pathway via the extrinsic pathway

- **Novel bypass therapies under development at Pfizer**
  - Engineered factor VIIa with improved therapeutic properties (in collaboration with Catalyst Biosciences)
  - “Zymogen-like” factor Xa as a novel approach to restore hemostasis (in collaboration with Children’s Hospital of Philadelphia)
Factor VIIa Molecules Generated Using a Rational Design Approach

- Structure and mechanism guided protein engineering to improve catalytic efficiency and duration of action for improved therapy

Increased potency and increased functional half-life
Factor VIIa Molecules Show Improved Potency in Human Hemophilia A and Hemophilia B Plasma

~ 5-10 fold more potent than rVIIa
An Engineered Factor VIIa Molecule Shows a Prolonged Duration of Action in Hemophilia A Mice

Dose: 3 mg/kg i.v.

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Summary of Rationally Designed FVIIa Molecules

- 5-10 fold increase in catalytic activity in several assays of factor Xa generation
  - Increased potency also seen in plasma-based assays

- Increased potency and prolonged duration of action seen in restoration of hemostasis in vivo
  - Genetic and induced models of hemophilia in mice

- Potential for more robust thrombin generation at a site of injury coupled with an increased duration of action
  - May significantly improve therapeutic outcomes for patients with inhibitors, including possibility for prophylactic therapy
Factor Xa is a Potential Bypass Therapy Since it Occupies a Central Position in the Coagulation Cascade

**Intrinsic Pathway**

- XII
- XIIa
- XI
- Xla
- IX
- IXa
- VIII
- VIIIa
- V
- Va

**Extrinsic Pathway**

- VII
- VIIa + TF (vascular injury)
- Xa
- Prothrombin
- Thrombin
- Fibrinogen
- Fibrin monomer
- XIII
- XIIIa
- Cross-linked fibrin polymer

It is the only activator of prothrombin.
Although the properties of Factor Xa had limited its therapeutic use, variants with desirable characteristics have now been designed.

- Zymogen-like activity in plasma, regulated by co-factor interaction at site of vascular injury
  - Decreased sensitivity to inhibitors as zymogen, until activated as prothrombinase

- Accomplished through disruption of normal zymogen to active enzyme transition by varying amino acids at new N-terminus responsible for insertion into active site

(courtesy of W. Bode)

Novel protein engineering approach that leverages detailed understanding of this mechanism.
Zymogen-like Activity Until Bound to Factor Va

Free Enzyme

Initial rate (mOD/min/nM E) vs Spectrozyme Xa (µM)

Prothrombinase

Initial rate (mOD/min/nM E) vs Spectrozyme Xa (µM)

Differential Sensitivity to Plasma Inhibitors (ATIII and TFPI)

Prolonged Half-life in Hemophilic Plasma

Hemophilia A Plasma

FXa\textsuperscript{I16L}

PD FXa
Key Data for Lead Candidate: “Zymogen-like” Factor Xa\textsuperscript{I16L}

- Zymogen-like behavior of free enzyme makes it less sensitive to endogenous inhibitors, as expected
- Extended half-life in human hemophilia A & B plasma
- Activity normalized when fully assembled in prothrombinase complex
  - Once assembled as prothrombinase, sensitive to inhibitors
- Restored thrombin generation in hemophilic plasma, comparable to rFVIIa
- Correction of prolonged bleeding time in both induced and genetic models of hemophilia in mice
  - No evidence of excessive activation of coagulation

Zymogen-like FXa variants also have potential for broad use as pan haemostatic agents.
Summary of Approaches to New Therapies

• Novel candidates with improved properties indicate promise as therapeutics to bypass upstream deficiencies of coagulation
  – Factor VIIa molecules generated using rational design
  – “Zymogen-like” factor Xa variants

• Integrated, structural approaches can significantly inform design of next generation replacement factors
  – Factor VIII and factor IX variants with extended duration of action through both protein engineering and formulation approaches

• Utilize details of activation, regulation, and clearance of these complex proteins to guide targeted modifications
Indication for XYNTHA

XYNTHA is indicated for the control and prevention of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency or classic hemophilia) and for surgical prophylaxis in patients with hemophilia A.

XYNTHA does not contain von Willebrand factor and, therefore, is not indicated in von Willebrand’s disease.
What is the Xyntha Prefilled Dual-Chamber Syringe?

Prefilled Dual-Chamber Syringe

- New delivery system
  - Available in 2010 in 3000 IU dosage
  - All strengths available in 2011
- Same quality attributes
  - Same drug substance and formulation
  - Low volume Diluent (4mL)
Key Benefits & Customer Feedback
• Key Benefits
  – Innovative, convenient system eliminates the transfer step during reconstitution
  – 3000 IU of Xyntha and 4mL of diluent supplied within device
  – Packaged as an all-in-one, travel-ready kit

…it eliminates the confusion of which pieces to put together and the order to put them in...especially in the clinic setting when time is of the essence and/or if it’s someone where we’re training our newer nurses, it’s easier to understand. Nurse, US

This, instead of having so many boxes out there, it comes in one kit. And that’s practical.” Caregiver, US

…it cuts down on all the different vials you have to deal with....Patient, US

“This is exactly what I wanted my device to be like; ... ready to be used and practical.” Pt, It
Important Safety Information for XYNTHA

- Anaphylaxis and severe hypersensitivity reactions are possible. Should such reactions occur, treatment with the product should be discontinued, and appropriate treatment should be administered.

- Patients using coagulation factor VIII products should be monitored for inhibitors, which have been detected in patients receiving factor VIII-containing products, including XYNTHA.

- The most common adverse reaction in study 1 (safety and efficacy study) is headache (24% of subjects) and in study 2 (surgery study) is fever (41% of subjects). The most common adverse reactions (≥5% of subjects) in clinical studies were headache, fever, nausea, diarrhea, vomiting, and weakness.

- Patients may develop hypersensitivity to hamster protein, which is present in trace amounts in XYNTHA.

- XYNTHA is an injectable medicine administered by intravenous (IV) infusion.

Please See full Prescribing Information available at this presentation
Support For Your Xyntha Patients

Trial Prescription Program

• Up to 20,000 IU of XYNTHA at no cost to the patient if the doctor decides XYNTHA is right for the patient

Factor Resource Program

A family of assistance programs for the uninsured and underinsured who need help getting Pfizer medicines.

Lifelines Ambassadors Program

A network of hemophilia patients willing to share their experiences with their disease & treatment with Pfizer factor replacement therapies to support others.

Pfizer